REMARKS

Claims 1-54 were submitted with the application as filed on January 3, 2006. In a concurrently-filed preliminary amendment, Applicants canceled claims 1-54 and added new claims 55 and 56. In their Second Preliminary Amendment, filed August 7, 2006, Applicants canceled claims 55 and 56 and added new claims 57-98. In their September 15, 2009 Response to a Restriction Requirement, Applicants elected without traverse Group V (claims 72-85 and 96, drawn to products of formula IV, formula V, formula VI, formula VII, and formula VIIa). In their March 25, 2010 Response to the first Office Action, Applicants amended claims 74, 77, and 78, and added new claim 99.

Currently, Applicants amend claims 82, 83, and 96, add new claims 100-135, and cancel claims 57-81, 84-85, 87-95, and 99. Claim 82 has been redrafted in independent form, the definition of A has been amended, the definition of R^g has been added, and the substituent R^{1d} has been expanded. Support for amended claim 82 may be found throughout the specification, and particularly at original claim 1, at page 18, at page 24, line 18 through page 25, line 15, and at page 27, line 26 through page 28, line 8. Claim 83 has been amended to include terminal punctuation, and to recite salts and N-oxides, as supported by claim 82. Claim 86 has been amended to depend from claim 82, and to recite salts and N-oxides, as supported by claim 82. New claims 100-119 ultimately depend from claim 82 and add limitations thereto. Support for the new claims may be found throughout the specification, including for example, at: page 20, lines 1-20 (claim 100); page 32, lines 22-23 (claim 101); page 36, lines 27-28 (claims 102-103 and 117-118); page 35, line 20 to page 36, line 4 (claim 104); page 36, lines 5-16 (claims 105-106); page 37, lines 5-10 (claims 107-108); page 33, lines 1-4 (claims 109-111); page 60, line 22 to page 63, line 15 (claim 112); page 64, line 20 to page 65, line 9 (claim 113); page 74, line 2 to page 75, line 19 (claim 114); page 59, line 11 (claims 115-116); and page 78, lines 21-22 (claim 119). Support for new claims 120-135 can be found in previously-pending claims 57, 61-68, and 87-93, as well as throughout the specification, including at pages 85-87 and 102. No new matter has been added. Claims 82-83, and 86, 96-98, and 100-135 are pending, although claims 86, 97-98, and 120-135 are withdrawn from consideration.

Applicants thank the Examiner for the telephone interview graciously granted on August 18, 2010, between the Examiner and Applicants' representative, Dr. Philip Hansen. The Examiner's Interview Summary adequately summarizes the substance of the interview, but out of an abundance of caution, Applicants submit a summary herewith.

The MPEP suggests that, to be complete, an interview summary must address the following issues. Applicants' summary follows each category.

(A) A brief description of the nature of any exhibit shown or any demonstration conducted – Not applicable

(B) Identification of the claims discussed – Claims in general, particularly claim 82.

(C) Identification of specific prior art discussed – Edwards *et al.* (WO 2003/035065).

(D) Identification of the principal proposed amendments of a substantive nature discussed, unless there are already described on the Interview Summary form completed by the examiner – Applicants proposed to narrow the scope of the pending claims to encompass the subject matter of claim 82 (with a proposed amendment to enlarge the scope of R^{1d}), which encompasses (morpholinylmethyl-benzimidazolyl)-pyrazolyl compounds.

(E) The general thrust of the principal arguments of the applicant and the examiner should also be identified –Applicants indicated that they would consider making a comparative showing to demonstrate unexpected advantages of compounds falling within the proposed amended claim scope over corresponding unsubstituted benzimidazole compounds found in Edwards. The Examiner indicated that she would review Edwards to determine the closest prior art compound, over which Applicants would be required to make a showing. On Friday, August 20th, the Examiner left Dr. Hansen a message indicating that if a comparison were to be made, it should be made over Edwards' examples A92-B32, A92-B36, A92-B89, A92-B96, and A92-B124, using Applicants' examples 203, 220, 283, and 299.

(F) A general indication of any other pertinent matters discussed – Not applicable.

(G) If appropriate, the general results or outcome of the interview – Not applicable.

The Examiner's rejections are addressed below. Reconsideration of the application and allowance of all claims pending herein are respectfully requested in view of the following remarks.

I. CLAIM REJECTIONS UNDER 35 U.S.C. § 112

A. Rejection of Claims 72-85, 96, and 99 for Lacking Enablement

The Office Action rejects claims 72-85, 96, and 99 under 35 U.S.C. § 112, first paragraph for allegedly lacking enablement. Specifically, the Action states that "while being enabling for a salt or N-oxide of the compounds, [the specification] does not reasonably provide enablement for a solvate of the compounds." While not acquiescing to this rejection, Applicants have, for the purpose of expediting prosecution, amended claim 82 by deleting "or solvate" from the claim. Applicants reserve the right to prosecute the deleted subject matter in a continuation application. Claims 72-81, 84-85, and 99 are canceled. Claims 83 and 96 depend from amended claim 82, which no longer recites solvates. Applicants respectfully submit that, in view of the instantly-made amendment, this rejection has been obviated.

B. Rejection of Claims 72-85, 96, and 99 for Being Indefinite

The Office Action rejects claims 72-85, 96, and 99 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Each of the Office Action's separate indefiniteness rejections are addressed below. For the following reasons, Applicants respectfully submit that the pending claims satisfy the definiteness requirement of 35 U.S.C. § 112, second paragraph.

a. Claims 72, 73, 77, and 78

Claims 72, 73, 77, and 78 are rejected for reciting "groups" in certain substituent definitions, instead of "group". Claims 72, 73, 77, and 78 have been canceled. Applicants have addressed each of the rejections in new claims 104, 109, 112, and 113.

b. Claim 73

Claim 73 is rejected for omitting an "or" and for lacking antecedent basis. Claim 73 has been canceled.

c. Claims 74 and 99

Claims 74 and 99 are rejected because the recitations "R^{1a}-NHC(=O)" and "R^{1b}-NHC(=O)" did not represent a urea in the group R^{1a}-A-NH. Claims 74 and 99 have been canceled.

d. Claim 78

Claim 78 is rejected for omitting recitations such as "or" and "and", for lacking antecedent basis, and for reciting "R^{6a} to R^{9a} include" instead of "R^{6a} to R^{9a} are each". Claim 78 has been canceled.

e. Claim 80

Claim 80 is rejected based on a lack of antecedent basis for the phrase "R^{11} and R^{12} together with the nitrogen atom form a five or six membered heterocyclic ring." Claim 80 has been canceled.

f. Claim 81

Claim 81 is rejected for omitting recitations of "and" in the substituent definitions, and for omitting dashes in certain substituent names. Claim 81 has been canceled. Applicants have addressed each of the rejections in new claim 112.

g. Claim 83

Claim 83 is rejected based on a failure to conform to MPEP § 608.01(m) due to the absence of a period at the end of the claim. Claim 83 has been amended to include a period.

h. Claims 84 and 85

Claims 84 and 85 are rejected for lacking antecedent basis, and for lacking a definition of the variable R^g. Claims 84 and 85 have been canceled. R^g is now defined in claim 82.

i. Claim 99

Claim 99 is rejected for failing to further limit claim 73. Claim 99 has been canceled.

II. Claim Rejections – Nonstatutory Double Patenting

The Office Action indicates that claims 72-85, 96, and 99 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-83, 104, 106-115 and 125-127 of co-pending Application No. 11/813,031. The Office Action states that "[t]his is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented" (Office Action, page 18). Due to the provisional nature of this rejection, in their March 25, 2010 Response, Applicants indicated that they would await the lifting of the provisional rejection until the claims are otherwise in condition for allowance. The instant Office Action asserts that "[i]n response, any arguments presented in the future will be deemed untimely."

Applicants respectfully traverse the assertion that any future arguments regarding the provisional non-statutory double-patenting rejection will be deemed untimely. The MPEP states that:

> Occasionally, the examiner becomes aware of two copending applications that were filed by the same inventive entity, or by different inventive entities having a common inventor, and/or by a common assignee, or that claim an invention resulting from activities undertaken within the scope of a joint research agreement as defined in 35 U.S.C. 103(c)(2) and (3), that would raise an issue of double patenting if one of the applications became a patent. Where this issue can be addressed without violating the confidential status of applications (35 U.S.C. 122), **the courts have sanctioned the practice of making applicant *aware* of the potential double patenting problem if one of the applications became a patent by permitting the examiner to make a "provisional" rejection on the**

> **ground of double patenting.** *In re Mott,* 539 F.2d 1291, 190 USPQ 536 (CCPA 1976); *In re Wetterau,*356 F.2d 556, 148 USPQ 499 (CCPA 1966). The merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to issue.
>
> **The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application** unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.

(MPEP § 804(I)(B)(emphasis added)). As explained above, the practice of making applicants *aware* of provisional nonstatutory double-patenting rejections is favored, and the provisional rejections *continue to be asserted* throughout prosecution until one of the applications issues to patent, or otherwise until no other remaining rejections are asserted.

MPEP §804(II), entitled "Requirements of a Double Patenting Rejection", further explains that a double-patenting rejection under nonstatutory grounds is only proper where "the grant of a patent with the claims in the application would unjustly extend the rights granted by the first **patent**". Since a patent has not yet issued in either of the involved applications, a nonstatutory double-patenting rejection is not yet proper. Further, because claims are frequently amended during prosecution, it would be unfair, inefficient, and often futile to require applicants to respond to a provisional double-patenting rejection. This is why the MPEP indicates that the provisional rejections "should continue to be made by the examiner in each application" (MPEP § 804(II)).

Indeed, relevant legal precedent has settled the issue by explaining that an applicant need not respond to provisional double-patenting rejections. For example, in *In re Mott* (539 F.2d 1291, 1296 (CCPA 1976)(which is cited in MPEP § 804)), an examiner had made a double-patenting rejection final even though both of the cited applications were pending. The CCPA reversed the double-patenting rejection, explaining that:

> We have trouble understanding the PTO's stated rationale for making the double patenting rejection final at this time. **Once the provisional rejection has been made, there is nothing the examiner and the applicant must do until the other application issues.** We see no undue burden here.

(*In re Mott*, 539 F.2d at 1296(emphasis added)). Consistent with relevant law and precedent, Applicants submit that they will await lifting of the provisional nonstatutory double-patenting rejection in the instant case until the claims are found allowable, or until the cited application issues. For the foregoing reasons, Applicants respectfully submit that a future-presented argument should be deemed timely.

III. PRIORITY

The Office Action states that the disclosures of the two U.S. provisional applications that the instant application claims the benefit of (60/484,685 and 60/514,374) were reviewed because of the possibility of intervening art. The Action asserts that not all claims of the instant application are sufficiently enabled by the provisional applications, and that therefore, those claims may only rely on the filing date of the PCT/GB04/02824 (July 5, 2004). The Action concludes that the anticipation rejection over Edwards *et al.* (WO 2003/035065), which was filed on October 24, 2002, applies.

In making the instant priority determination, the Office Action indicates that Applicants' provisional applications failed to provide adequate support or enablement for one or more claims of the instant application. Variables R^{6a}-R^{9a} (which are absent from the amended claim set as presented herein) are particularly mentioned.

Where an application claims the benefit of a provisional application, the effective filing date "is the filing date of the provisional application for any claims which are fully supported under the first paragraph of 35 U.S.C. 112 by the provisional application." (MPEP §706.02(VI)(D)). Applicants submit that the effective filing date for each pending claim herein is the filing date of the earliest provisional application within which support for the claim may be found.

IV. CLAIM REJECTIONS UNDER 35 U.S.C. § 102

The Office Action rejects claims 72, 74, 78, 80, 81, and 96 under 35 U.S.C. § 102(b) as being anticipated by Edwards *et al.* (WO 2003/035065)(hereinafter referred to as "Edwards"). In order to anticipate a claim, a reference must set forth each and every element of the claim (*see* MPEP § 2131). Claims 72, 74, 78, 80, and 81 have been canceled, and claim 96 has been amended to depend from claim 82, which was not subject to the anticipation rejection. Applicants respectfully submit that the cited Edwards compounds do not fall within the currently-claimed genus, and therefore do not anticipate Applicants' claims (*see* MPEP 2131.02).

V. CLAIM REJECTIONS UNDER 35 U.S.C. § 103

The Office Action rejects claims 72-85, 96, and 99 under 35 U.S.C. § 103(a) as being obvious over Edwards. Specifically, the Office Action states that

> Applicant claims 2-(pyrazol-3-yl)benzimidazole compounds. Edwards et al. (see entire document; particularly pages 4-9, 26-29, 42-59, 94-199 and 245-247; and especially the compound on page 210, line 4; the compound on page 203, line 35; compound A6-B39 and compound A6-B40 on page 114; compound A7-B39 and compound A7-B40 on page 115; compound A91-B39 and compound A91-B40 on page 183; compound A92-B39 and compound A92-B40 on page 183; compound A93-B39 and compound A93-B40 on page 184; and Compound 248(f) on page 421) teach 2-(pyrazol-3-yl)benzimidazole compounds that are either structurally the same as…or structurally similar to the instant claimed compounds.

(Office Action, pages 24-25). The Office Action further states that:

> …The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (e.g., protein kinase inhibitors).
>
> One skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating, for example, asthma and cancers. The instant claimed invention would have been suggested to one skilled in the art

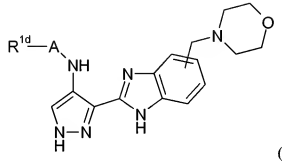
and therefore, the instant claimed invention would have been obvious to one skilled in the art.

(Office Action, page 26).

Claims 72-81, 84-85, and 99 have been canceled. For the following reasons, Applicants respectfully traverse the obviousness rejection of claims 82-83 and 96.

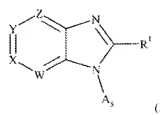
1. **Introductory Matter: Differences Between the Present Invention and the Cited Prior Art**

As a preliminary matter, Applicants point out that the present invention, as recited in amended independent claim 82, relates to (morpholinylmethyl-benzimidazolyl)-pyrazolyl compounds of formula (VII):



(VII)

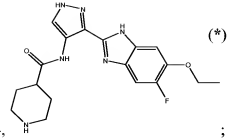
Edwards, on the other hand, discloses compounds containing the general structural formula **(1x)**:

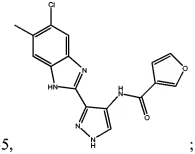


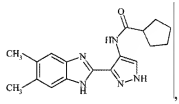
(1x)

Of the compounds mentioned in the obviousness rejection in the instant Office Action, Edwards only asserts to have actually made the following:

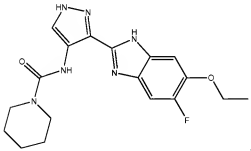
(*)

(1) the compound on page 210, line 4,  ;

(2) the compound on page 203, line 35,  ; and

(3) compound 248(f) on page 421  ,

(*) However, Applicants note that the synthesis of the compound listed on page 210, line 4, "piperidine-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide" is questionable. This compound *name* appears on Edwards' page 446 as Example 527(d), although the corresponding *structure* is shown as a nitrogen-attached piperidine-**1**-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide:



. Going back to the starting material (*see* Edwards, page 542, example 48(g)), the *name* is a piperidine-**4** compound, but the corresponding *structure* is a piperidine-**1**, and the starting material is listed as piperidine-**1**-carbonyl chloride. In view of the several inconsistencies, a skilled artisan would question whether Edwards was actually in

possession of piperidine-4-carboxylic acid [3-(6-ethoxy-5-fluoro-1H-benzimidazol-2-yl)-1H-pyrazol-4-yl]amide, and would likely disregard the compound. See, for example, *In re Yale* (434 F.2d 666 (CCPA 1970)), which dealt with a typographical error that was obvious to a skilled artisan, which resulted in an erroneous listing of a compound. The CCPA found that:

> Since it is an obvious error, it cannot be said that one of ordinary skill in the art would do anything more than mentally disregard CF(3) CF(2) CHClBr as a misprint or mentally substitute CF(3) CHClBr in its place. Certainly he would not be led by the typographical error to use the erroneous compound as an anesthetic even if as a chemist of ordinary skill in the art he would know how to prepare the compound.

(*In re Yale,* 434 F.2d at 668-669).

2. A *Prima Facie* Case of Obviousness Has Not Been Established

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference(s) must teach or suggest all the claim limitations. (MPEP § 2143). Applicants respectfully assert that a *prima facie* case of obviousness has not been established because, *inter alia*, a skilled artisan would have no reason to modify Edwards to arrive at Applicants' claimed invention.

As discussed above, Edwards teaches a genus of formula (1x), which encompasses an enormous breadth of compounds. The Office Action asserts that "the instant claimed compounds are generically described in the prior art" (Office Action, page 25). A USPTO examiner described the breadth of Edwards' genus in a corresponding U.S. application as being so large that it was impossible to even determine what subject matter was included or excluded (*see* Dec. 4, 2003 Office Action, issued in connection with U.S. application no. 10/279,834, p. 4). Applicants do not disagree with the instant Office Action insofar as it states that "considerations and determinations of patentability of claims in another application has no relevancy in the consideration and determination of patentability of claims in the instant application" (Office

Action, page 28). However, Applicants submit that the description of Edwards' genus (as being of such vast breadth that it was impossible to determine what subject matter was included or excluded), is indicative of the fact that a person having ordinary skill in the art would, just as the U.S. examiner did, consider Edwards' enormous disclosure to significantly exceed the scope of the enabled invention.

Applicants submit that upon reading Edwards' 701 page disclosure, a person having ordinary skill in the art would first try to identify what Edwards made. Indeed, preceding the synthesized examples, Edwards indicates that the "invention is further exemplified but not limited by the following illustrative Examples and Reference Examples" (Edwards, page 274, lines 1-2). Edwards discloses hundreds of synthesized examples, all having significantly different structures than those which Applicants currently claim.

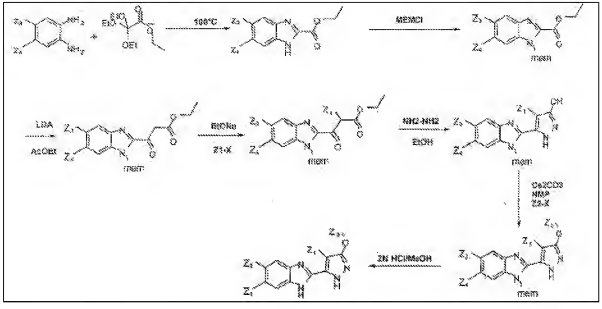
To identify the compounds of interest, a person having ordinary skill in the art would next attempt to determine which of Edwards' compounds had the best activities. Edwards states that Tables 5 and 6 show the pharmacological "results obtained in the above tests for the products indicated as examples in the present application" (*see* Edwards, pp. 561 and 563). Together, Tables 5 and 6 provide data for 221 examples that were tested for their ability to inhibit phosphorylation of PLCγ by KDR. Upon reviewing these data, a person having ordinary skill in the art would note, among other things, that *all* of Edwards' species with the greatest activities (lowest IC_{50} values) have core structures that are 3-(benzimidazol-2-yl)-indazoles, which are significantly different from Applicants' instantly-claimed compounds.

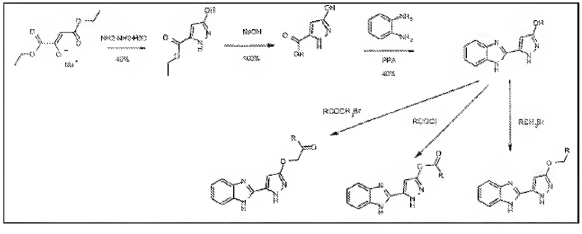
The Office Action asserts that "[o]ne skilled in the art would thus be motivated to prepare products embraced by the prior art to arrive at the instant claimed products with the expectation of obtaining additional beneficial products which would be useful in treating, for example, asthma and cancers" (Office Action, page 26). However, as discussed above, Applicants respectfully submit that a person having ordinary skill in the art would readily appreciate that Edwards' 3-(benzimidazol-2-yl)-*indazole* compounds had the best activities. There is no motivation to select a *pyrazole* compound, and to make the significant modifications that would be required to arrive at Applicants' invention. In fact, as explained more comprehensively

below, Applicants submit that the Edwards disclosure would actually *dissuade* one from making the proposed modifications.

Edwards' Table 5 shows quantitative activity data for 20 compounds that Edwards tested (*see* Edwards, pages 561-562). Consistent with Edwards' focus, all of the 20 compounds are benzimidazolyl-indazoles, except for examples 20, 21, and 23, which are 2H-pyrazol-3-yl-1H-benzimidazoles. The three pyrazole-containing examples (20, 21, and 23) all exhibited extremely poor activity, with example 21 having the worst activity out of all of the compounds in the entire table. Table 6 does not provide IC_{50} values, but it indicates that none of the tested pyrazole compounds (examples 181-228) had good activity ($IC_{50} <$ 0.3 μM- *see* Edwards, page 563, line 6). In view of the poor pharmacological activity of the pyrazolyl-benzimidazoles (and the much better performance of the indazolyl-benzimidazoles), Applicants submit that a person having ordinary skill in the art would be dissuaded from selecting a pyrazole compound as the subject for further modifications. If an artisan were motivated, as the Office Action suggests, to undertake experimentation because of their "expectation of obtaining additional beneficial products", they would start with a product having an indazolyl-benzimidazole core, since those are clearly and unambiguously taught to have the best pharmacological activity.

Moreover, Applicants submit that even if a person having ordinary skill in the art were to start with one of Edwards' pyrazolyl-benzimidazole compounds, there would be no motivation to modify it to arrive at Applicants' claimed invention. Edwards explains that the pyrazolyl-benzimidazole examples can be prepared according to the following schemes:





(*See* Edwards, page 361). The second scheme may be used only where the benzimidazole is unsubstituted, which would exclude all of Applicants' claimed compounds, since they require a morpholinylmethyl group to be attached to the 4, 5, 6, or 7 position of the benzimidazole. To synthesize Applicants' claimed compounds in accordance with Edwards' first scheme, one would have to use (morpholinylmethyl)benzene-1,2-diamine as a starting material. Applicants submit that a person having ordinary skill in the art would have no motivation to make this modification. In fact, one would likely be dissuaded, or at least hesitant to use such a starting

material because the basicity of the morpholinyl nitrogen could interfere in subsequent alkylating steps.

In describing the requirements for a *prima facie* case of obviousness for a chemical compound, the Federal Circuit has explained that:

> ...Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon,* 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak,* 769 F.2d 729, 731-32 (Fed.Cir.1985).
>
> We elaborated on this requirement in the case of *In re Deuel,* 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.,* an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* **A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."** *Id.* **We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.** *Id.* (citing *In re Jones,* 958 F.2d 347 (Fed.Cir.1992); *Dillon,* 919 F.2d 688; *Grabiak,* 769 F.2d 729; *In re Lalu,* 747 F.2d 703 (Fed.Cir.1984)).
>
> That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR... **Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.**

(*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007)). The requirement for a motivation to modify a chemical compound was more recently confirmed by the Federal Circuit in *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999, (Fed. Cir. 2009), where the court articulated that:

> Thus, to establish a prima facie case of obviousness in cases involving new chemical compounds, the accused infringer **must identify some reason that would have led a chemist to modify a known compound in a particular manner.** *See Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.,* 231 F.3d 1339, 1344 (Fed.Cir.2000). This standard is consistent with the legal principles announced in the Supreme Court's decision in *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.,* 492 F.3d 1350, 1356 (Fed.Cir.2007); *Eisai,* 533 F.3d at 1359 ("**In other words, post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.**").

(*Altana Pharma AG*, 566 F.3d at 1007). Applicants submit that Edwards fails to provide the required *reason* or *motivation* for a skilled artisan to make the modifications necessary to arrive at Applicants' invention. Moreover, in the above passage, the Federal Circuit cites to its decision from *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008) to support the proposition that "a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound." This precedent supports Applicants' argument that a skilled artisan would select compounds having good activity from the Edwards' disclosure for further modification, as opposed to choosing untested compounds (especially when tested compounds sharing similar core structures exhibited poor activities).

Indeed, in *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007), Alphapharm argued that Takeda's claims were obvious because prior art would have led a skilled artisan to select a certain compound as a "lead compound" to modify in order to improve upon its activity. Even though in *Takeda* (unlike in the instant case), the selected compound was highly active, the Court held that a *prima facie* case of obviousness had not been established because the art did not provide any reason to make the specific modifications required to arrive at Takeda's claimed invention. Likewise, Applicants submit that a *prima facie*

case of obviousness has not been made in the instant case because there is no reason to select compounds having poor activity as targets for further modifications, let alone to make the specific modifications required to arrive at Applicants' claimed compounds.

Applicants further assert that a person having ordinary skill in the art would not undertake a review of the seemingly endless combinations listed in Edwards' table, to arbitrarily select combinations for further testing. Instead, as described above, an artisan would more likely look to see what Edwards made, would seek out the most active compounds, would appreciate that they are all indazolyl-benzimidazoles, and would choose as a starting point for further testing a compound having shared characteristics with Edwards' active examples.

In making the enablement rejection against Applicants' claims, the Office Action states that:

> "As was stated in *Morton International Inc v. Cardinal Chemical Co.* 28 USPQ2d 1190 at page 1194: 'The specification purports to teach with over fifty examples, the preparation of the claimed compounds with the required connectivity. **However...there is no evidence that such compounds exist**... the examples of the '881 patent do not produce the postulated compounds... there is...no evidence that such compounds even exist.' ...Note that in *University of Rochester v. G.D.Searle & CO.* 68 USPQ2d 1424 at 1438 **the screening for over 600 compounds was deemed to be undue**. Applicant's claimed scope of compounds far exceeds this number"

(Office Action, pages 10-11). Applicants cannot help but to apply the above language to the Edwards disclosure. As discussed below, there is no evidence that the compounds in Edwards' table even exist. The Office Action cites precedent that indicates that screening for over *600* compounds was deemed to be undue, yet the Examiner has chosen five combinatorial artifacts from a table that includes **18,590** combinations. Surely, it must be considered undue experimentation for a person having ordinary skill in the art to go through *18,590* theoretical compounds, and to modify them so as to arrive at Applicants' invention. Applicants submit that the above-described course of seeking out the active compounds is a much more appropriate, realistic, and likely approach.

In her Interview Summary, the Examiner concludes that Edwards' morpholinylamide combinations A92-B32, A92-B36, A92-B89, A92-B96, and A92-B124 are the closest prior art examples to Applicants' claimed compounds. Applicants respectfully submit that since there is no indication that these theoretical compounds even exist, and because taken as a whole, Edwards' disclosure does not fairly suggest any *desirability* of these compounds, let alone any motivation to modify them to arrive at Applicants' invention, they cannot support an obviousness rejection.

Indeed, in *In re Wiggins*, 488 F.2d 538, 543-44 (CCPA 1973), the examiner rejected an applicant's claims over an article by Guidicelli *et al.* in view of a patent to Donnison. Wiggins' application was directed to certain barbituric acid derivatives. Guidicelli reported the preparation of a number of oxobarbituric acid derivatives. The CCPA noted that, as in the instant case, "*[n]one* of the compounds actually prepared and studied [by Guidicelli] fall within the scope of the [Wiggins'] claims" (*In re Wiggins*, 488 F.2d at 542). However, Giudicelli mentioned by name two compounds that did fall within Wiggins' claims. Noting that Guidicelli had failed to synthesize these claims, for enablement, the examiner cited a second prior art reference, Donnison, which disclosed a process similar to that of Wiggins for making oxo- and thiobarbituric acids (*see id.*). The CCPA reversed the examiner's rejection, explaining that:

> ...We do not accept this presumption ["that the naming of the compounds by Giudicelli constitutes a description of the invention within the meaning of § 102(b)"]. In our view, **Giudicelli's listing of the compounds by name constituted nothing more than speculation about their potential or theoretical existence.** The mere naming of a compound in a reference, without more, cannot constitute a description of the compound, particularly when, as in this case, the evidence of record suggests that a method suitable for its preparation was not developed until a date later than that of the reference.
>
> **If we were to hold otherwise, lists of thousands of theoretically possible compounds could be generated and published which, assuming it would be within the level of skill in the art to make them, would bar a patent to the actual discoverer of a named compound no matter how beneficial to mankind it might be. In view of the fact that the purpose sought to be effectuated by the patent law is the encouragement of innovation, such a result would be repugnant to the statute.** Therefore, we hold that the

> compounds named in Giudicelli and within the scope of the claims in issue were not "described in a printed publication" as meant by the applicable portion of § 102(b). This dictates a reversal of the rejection of claims 1, 2 and 10 under that section.
>
> Our holding does not mean that a reference merely naming a compound is without effect at all. It may be used as evidence of obviousness under § 103 for all it fairly suggests to one of ordinary skill in the art.

(*In re Wiggins*, 488 F.2d at 543-44 (CCPA 1973)). Consistent with *In re Wiggins,* Applicants submit that holding a handful of the 18,590 compounds (which, unlike in *Wiggins,* do not even fall within Applicants' claim scope) from Edwards' table against Applicants' invention would be repugnant to the patent statute because it would *prima facie* bar a patent to the actual discoverer of a named compound. The Examiner has pulled the five Edwards' combinations from a table that recites every *single* combination of 110 "A" groups with 169 "B" groups. The table itself begins on page 110 and spans 89 pages. It includes **18,590** combinatorial artifacts. This is a worst-case scenario of the type of "list[] of thousands of theoretically possible compounds" that the CCPA worried about in *In re Wiggins.* Indeed, *Wiggins* clearly states that a mere listing of compounds, which constitutes nothing more than speculation about their potential or theoretical existence, will not be considered to be disclosed, since the compounds do not necessary even exist. This applies to the instant situation, and to the 18,590 theoretical combinations listed in Edwards' 89 page-long table, which, just like the entirety of the Edwards disclosure, provides no motivation to make the necessary modifications to arrive at Applicants' invention, including, for example, the modification to add a morpholinylmethyl group.

As evidence of the unexpected activity of the morpholinylmethyl group, Applicants submit herewith, and incorporate herein by reference, the Declaration of Dr. David Charles Rees (the "Rees Declaration"). Dr. Rees is the Senior Vice President of Astex Therapeutics Limited, the Assignee of the instant application. As indicated in the Rees Declaration, test data indicate that introduction of the morpholinylmethyl group leads to a substantially increased activity against Aurora kinase activity and the human colon carcinoma cell line HCT116 (*see* Rees Declaration, pages 3 and 8).

The Rees Declaration includes cell assay data showing that when Applicants' morpholinylmethyl-substituted compound 8 was compared to the corresponding unsubstituted compound 7, the morpholinylmethyl compound was found to be about *30 times as active* (*see* Rees Declaration, pages 2-3). Morpholinylmethyl-substituted example 22 was also far more active than compounds of Examples 6, 73, and 84 (*see* Rees Declaration, pages 4-5). Table C of the Rees Declaration provides additional comparative data of morpholinylmethyl-substituted compounds over unsubstituted benzimidazole compounds, which even further demonstrate the improvement in cellular activity arising from the presence of a morpholinylmethyl side chain.

Critically, the Rees Declaration also provides data (*see, e.g.,* Table D and Table E) comparing compounds bearing a morpholinylmethyl side chain, which exhibit basic properties, with compounds bearing a morpholinylamide side chain, (a substituent shared by *all* of the Edwards combinations cited in the Examiner's Interview Summary, A92-B32, A92-B36, A92-B89, A92-B96, and A92-B124), which, in contrast, do not. The cell assay data show that in each case, the compounds bearing the morpholinylmethyl side chain are more active than those bearing the morpholinylamide side chain. These data demonstrate the importance of Applicants' morpholinylmethyl substituent, as compared to the morpholinylamide that is found in Edwards' cited theoretical compounds, where the nitrogen is not basic because instead, it is functionally an amide.

Through the data presented herein, Applicants have demonstrated the unexpected advantageousness of their morpholinylmethyl substituent, which has been proven to have better activity than morpholinylamides, such as the cited Edwards combinations. Applicants have also established that there is no motivation to modify Edwards to arrive at Applicants' invention. Edwards teaches that his most active compounds are benzimidazolyl-indazoles, and his test data indicate poor activity for benzimidazolyl-pyrazoles. Upon reading Edwards, a skilled artisan would have no reason to modify the core structures of the active compounds from benzimidazolyl-indazoles to the less active benzimidazolyl-pyrazoles, and would further have no reason to then add a morpholinylmethyl side chain.

In view of the foregoing, Applicants respectfully assert that a person having ordinary skill in the art would not consider the Edwards reference to teach or suggest the instantly claimed

compounds. As MPEP § 2144.08(II) provides, "[t]he fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." The very large size of Edwards' formula **(1x)** genus (*see* MPEP § 2144.08(II)(A)(4)(a)), together with the fact that all of the most active embodiments are different in structure from the claimed genus (*see* MPEP § 2144.08(II)(A)(4)(c)), together with the teaching away arguments presented above, weigh against a determination of obviousness (*see* id. (citing *Baird,* 16 F.3d at 382-383 (reversing obviousness rejection of species in view of large size of genus and disclosed "optimum" species))). Applicants respectfully assert that there is no motivation to modify Edwards to arrive at Applicants' invention, and therefore, a *prima facie* case of obviousness has not been established.

3. The Instant Obviousness Rejection Over Edwards Is Based on Impermissible Hindsight and is Thus Improper

Applicants further traverse the instant rejection because it is based on impermissible hindsight. The MPEP provides that "[i]t is difficult but necessary that the decision maker forget what he or she has been taught . . . about the claimed invention and cast the mind back to the time the invention was made (often as here many years), to occupy the mind of one skilled in the art." (MPEP § 2141.01(III) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)).

Applicants respectfully submit that the proposed modifications to Edwards to arrive at Applicants' claimed invention (including, for example, choosing a pyrazolyl-benzimidazole core, even though all such compounds in Edwards had poor activity, and modifying them to include a morpholinylmethyl group in the absence of any reason to do so, and despite possible synthesis dilemmas associated with such a modification), are improper because the Office Action relies on information gleaned solely from Applicants' specification. MPEP § 2142 states that "**impermissible hindsight must be avoided** and the legal conclusion must be reached on the basis of the facts gleaned from the prior art" (emphasis added). "Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's

disclosure, such a reconstruction is proper." MPEP § 2145(X)(A), (quoting *In re McLaughl*in, 443 F.2d 1392, 1395 (CCPA 1971)).

In the present case, the Office Action relies primarily on Edwards' teaching of an enormous genus to arrive at proposed modifications that skilled artisans would allegedly make to a handful of combinations that one could arbitrarily select from a list of over eighteen thousand. The Office Action states that a skilled artisan would be motivated to modify Edwards because of the expectation of obtaining additional beneficial products. Applicants respectfully question where this motivation comes from. Indeed, why would someone have such an expectation when the core structures they would allegedly choose to modify were all shown to have poor activity in the cited reference? (Especially when the cited reference clearly teaches better structures that exhibit very good activity?) The notion of active, morpholinylmethyl-substituted benzimidazole kinase inhibitors **is absent from the cited art** and is only present in Applicants' specification. Due to the lack of any reasoning whatsoever in the cited art and the fact that it arguably teaches away from the proposed modifications, it logically follows that the proposed rationale to modify Edwards has been improperly gleaned from Applicants' own specification, and that the modification is an exercise of impermissible hindsight. Accordingly, it is respectfully submitted that the suggested modifications to Edwards are improper.

VI. CONCLUSION

In view of the foregoing, reconsideration and withdrawal of the rejections are respectfully requested.

No fees are believed due. However, the Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment, to Deposit Account No. 08-1935, Reference No. 3073.004A.

There being no other outstanding issues, it is believed that the application is in condition for allowance, and such action is respectfully requested.

If a telephone conference would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone her at the number provided.

Respectfully submitted,

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